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Effect of Low Amphetamine Doses on Cardiac Responses to Emotional Stress in Aged Rats

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NYAKAS, C., B. BUWALDA, P. G. M. LUITEN AND B. BOHUS. *Effect of low amphetamine doses on cardiac responses to emotional stress in aged rats.* NEUROBIOL AGING 13(1) 123–129, 1992.—In young Wistar rats conditioned emotional stress can be characterized by a learned bradycardiac response to an inescapable footshock. In aged rats this bradycardiac response is attenuated and accompanied by suppressed behavioral arousal in response to novelty. In the present study, cardiac responses to emotional stress and behavioral reactivity to a novel experience in an open field were tested in aged and young rats under the influence of a low dose of d-amphetamine (AMPH, 0.5 mg/kg IP). AMPH administration in 27-month-old rats reinstated the bradycardiac response to emotional stress, while it failed to influence the resting heart rate in the home cage. Age-associated differences in open-field ambulation, present in drug-free conditions, were antagonized by low doses of AMPH (0.25–1.0 mg/kg). It is concluded that enhanced arousal by aminergic stimulation with AMPH in the aged rat invoked cardiac and behavioral response patterns resembling those at younger ages.

Aging Bradycardiac response Behavioral arousal Amphetamine Stress

PREVIOUS studies in this laboratory on young male Wistar rats have shown that exposure to certain types of emotional stress, i.e., to expectancy of an unavoidable footshock, leads to a characteristic, bradycardiac heart rate response (2, 3, 18, 27). This deceleratory type of conditioned cardiac response diminishes with age; it is reduced over one year of age, and is practically absent in aged and senescent rats (27). The behavioral characteristics of aged rats in stress conditions like novelty-induced arousal also differ from that of young ones. Depending on the experimental circumstances it either shows a delayed appearance (5) or is reduced as compared to young age (16,34). Old rats respond to stress with a delay in the increment of brain noradrenergic activity as compared to young controls (19), and consistently show a reduced response of brainstem and forebrain noradrenergic systems shortly after stress (32,36). The absence of a vagally mediated cardiac response to emotional stress in aged rats is likely to be related to deficient neuronal processing in arousal mechanisms. There is growing evidence for a common neural network including catecholaminergic pathways mediating both arousal and vagally evoked bradycardiac responses (4, 9, 13, 15, 35, 37). Thus a delayed response of neurotransmitter systems supporting arousal, e.g., from the ascending catecholaminergic system (21, 30, 36), may be part of the mechanism underlying the altered stress response in aging. The view that aged rats are potentially capable to perform physiological responses well comparable to young animals is supported by the finding that movement disorders of aged rats can be reversed by central dopamine receptor stimulation (24). Consequently, we assumed that by increasing the level of arousal, a reinstatement or enhancement of the conditioned bradycardiac stress response may be obtained in aged rats. Such an increased arousal level was achieved by application of the psychostimulant amphetamine (AMPH).

AMPH in low doses is known to elicit behavioral activation and to enhance performance in learned tasks without provoking overt stereotyped behavioral movements (7, 11, 12, 23). This effect is considered to be mainly mediated through dopaminergic and to a lesser degree through noradrenergic neurons (20, 23, 25, 26).

Thus the aim of the present experiments was first: to study the cardiac and behavioral response of aged Wistar rats to emotional stress under the influence of a low dose of AMPH. Two age groups were compared, 27 and 5 month old, representing the aged and young life conditions in rats, respectively. The emotional stress condition was generated in a step-through type passive avoidance learning situation. Fear of punishment was induced by exposing the rat to the compartment in which an unavoidable, painful footshock was given the previous day.

The second objective of this study was to establish the optimal dose of AMPH. The dose-dependent impact of AMPH administration was investigated on the response of the experimental animals in a novelty-induced arousal test in a small open field.

The third question to answer dealt with the age-dependency of behavioral motor activation by AMPH in the open-field mobility test.

METHOD

Animals

The majority of the observations were carried out on two groups of male Wistar rats of 5 and 27 months of age. The age-dependency of the AMPH effects was studied in two additional age groups of 21 and 33 months. The animals originated from the Ivanova substrain and were kindly donated by Merck, Darmstadt, Germany. All rats were housed in groups of 4 or 5 ani-

imals in a light-controlled room (lights on from 07:00 to 19:00 hours). After implantation of two subcutaneous stainless steel electrodes for electrocardiogram (ECG) recording (2), each rat was individually housed in a quadrangular Plexiglas cage. Food and water were supplied ad lib. All experiments were performed between 09:00 to 13:00 hours.

Dose- and Age-Dependency of AMPH Effects

Dose-dependency of AMPH effects. An initial open-field behavior experiment was carried out to assess the dose-dependent behavioral effects of AMPH and to select an optimal dose for the subsequent experiments. The dose-dependent change of behavioral response to AMPH was compared in aged (27-month-old) vs. young (5-month-old) rats.

d-Amphetamine sulfate (OPG, Utrecht, The Netherlands) dissolved in physiological saline was injected IP in a dose range of 0.05, 0.25, and 1.0 mg/kg body weight. Controls were injected with the saline solution. Drugs and saline were administered in an injection schedule of a random crossover design to the same group of 7 rats per age. In this design drug and saline injections were alternated. Furthermore, a two-day washout period was allowed between two injections after AMPH was given.

The AMPH effects were assessed by measuring novelty-induced behavioral arousal in a small open field (SOF). A rectangular box with transparent walls (20×20×30 cm; 1×w×h) served as the SOF. Behavioral activities were scored every 15 s during a period of 60 min, with a parallel observation of 8 rats. The following behavioral items were distinguished: rearing, walking, head turning with sniffing (ambulatory and exploratory types of movements here called locomotion for the sake of simplicity), face washing, licking of the body hair (elements of grooming), and immobility or sleep.

Age-dependency of AMPH effects. Based on the experience obtained in the previous experiment, the age-dependency of the AMPH effects in the open-field test were assessed by applying a single selected optimal dose of 0.5 mg/kg AMPH. The behavioral response to AMPH and saline treatment in the SOF was quantitatively analyzed in young and in two additional aged groups of 21 and 33 months.

In all SOF tests drugs or saline were administered 10 min before the start of the 1-h observation period.

Heart Rate and Behavior in Stress and Rest Conditions

Experimental procedure in the stress condition. A one-trial learning paradigm in a step-through passive avoidance test (1) was used to investigate the cardiac and behavioral response to emotional stress. The experimental procedure started with habituation to experimental circumstances as well as to intraperitoneal injections with saline (see experimental protocol in Fig. 1). The experimental procedure included 1) fixing of a belt around the chest to hold a miniature radio transmitter (3 g), 2) carrying the rat from the home cage to the experimental room, and 3) placing the animal into a waiting cage for one minute. The waiting cage was located next to an experimental box designed for passive avoidance training. The passive avoidance setup consisted of a large black box or shock-compartment, in which an electric footshock could be delivered through the wiring of a grid floor. First the rat was placed onto a well-lit narrow platform attached to the dark shock-compartment. The rat could enter the dark through a small door to avoid intense light while staying on the platform. When the rat entered the dark-compartment, the sliding door was closed and the animal allowed to ex-

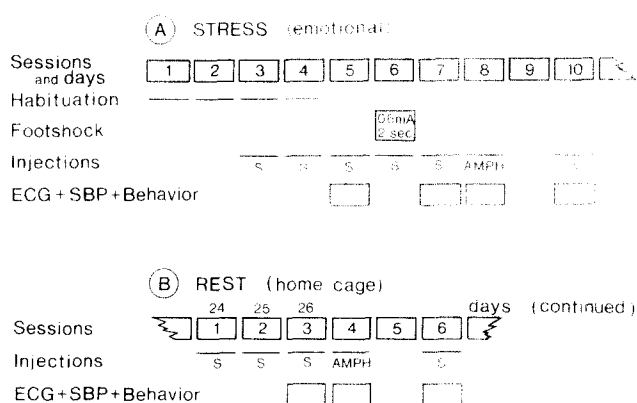


FIG. 1. Experimental protocol for sampling electrocardiograms (ECG), systolic blood pressure (SBP), and behavioral activity measurements in (A) emotional stress (dark-compartment of a passive avoidance apparatus) and (B) rest conditions. S: saline injection, AMPH: 0.5 mg/kg d-amphetamine sulfate.

plore the dark chamber for 5 min. This procedure was repeated throughout 4 daily sessions. Beginning with the third session, 20 min before each transport to the experimental room, a saline injection was given intraperitoneally. At the 5th daily session, ECG measurements were started to obtain "preshock" values, i.e., control heart rate values prior to generating a one-trial learning fear reaction in the avoidance situation. ECG recordings started directly upon entrance in the dark-compartment and lasted for a period of 1 minute. On day 6 an inescapable electric footshock (0.6 mA, 2 s) was delivered immediately after entering the dark-compartment. The rat was removed after 1 min and returned to the home cage. To obtain "postshock" ECG values, the rats were subjected to the experimental situation on days 7, 8, and 10. In all three daily sessions ECG's were recorded as described above. On day 8 rats were injected with AMPH in a dose of 0.5 mg/kg b.wt., IP, 20 min before transport to the experimental room. On days 7 and 10 the same animals were injected with saline.

During ECG measurements the duration of exploratory types of movements were recorded. These movements were: rearing, walking, and head movements with sniffing. The behavioral activity time was processed for data analysis.

Experimental procedure in the rest condition. Two weeks after the completion of studies in the stress condition, the resting heart rate and behavioral reactivity to AMPH were recorded in the home cage. The experimental procedure lasted for 6 days. Seven rats per group received a saline injection at sessions 1, 2, 3 and 6, 20 min before ECG and behavioral recordings. AMPH was injected IP in a dose of 0.5 mg/kg b.wt. on session 4. The ECG and behavioral samplings of 1 min were carried out at sessions 3, 4, and 6. The behavioral activity was measured in seconds.

Recording and analysis of ECG. The electrocardiogram (ECG) of freely moving animals was monitored by means of a miniature FM transmitter (model SNR 102F, Dynamic Electronics Ltd., London, England) as described earlier (2). Briefly, the transmitter was attached to a velcro strap secured around the thorax of the rat. The transmitter was connected to the two transcutaneous electrodes. The transmitted signals were received on a commercial FM receiver, amplified with half-amplitude cut-off frequencies at 10 and 100 Hz (Grass P5CR preamplifier) and stored on tape (Minilog, Philips).

For computer analysis the prerecorded ECG samples were played back through a cardi tachometer pulse generator, which generated a square wave pulse at each R wave. The original ECG recording and the generated R wave pulses were visualized on an storage oscilloscope for visual control. The time between the onset of two consecutive pulses, defined as interbeat interval (IBI) was measured by a personal computer (Olivetti M24) equipped with an interface. The IBIs falling within the range of 100 to 220 ms have been selected for computing the mean IBI of each sampled period.

Systolic blood pressure. Blood pressure was measured noninvasively either immediately after the ECG sampling in the emotional stress situation or after the one minute ECG and behavioral recordings in the home cage. The systolic blood pressure (SBP) measurement was carried out under light ether anesthesia with the tail-cuff method using a photoelectric sensor unit to detect arterial pulses visualized on an oscilloscope. The pressure in the cuff placed around the base of tail was gradually elevated till the disappearance of pulsation. During gradual decreasing of the pressure the SBP was read on a manometer at the moment of the reappearance of pulses and expressed in mmHg.

Statistical analysis. For the statistical evaluation of the data two-factor analysis of variance (ANOVA) with or without repeated measures was applied according to the STATS PC program. Post hoc pairwise comparisons between two groups was carried out by *t*-test corrected for repeated comparisons as appropriate. The paired *t*-test was used after ANOVA with repeated measurement on one factor.

RESULTS

Dose- and Age-Dependency of AMPH Effects on Novelty-Induced Behavioral Activation

The dose-dependency of changes in behavioral activation after AMPH treatment were tested in a small open field. Both locomotion and grooming of 5- and 27-month-old rats showed dose-dependent changes (Fig. 2). Two-factor ANOVA with repeated measures showed that the smallest dose used (0.05 mg/kg) already significantly increased locomotor activity, $F(1,12) = 5.01$, $p < 0.05$. The dose-dependent increase in locomotion was highly significant in both age groups ($p < 0.001$). The baseline difference between the two age groups (0.0 mg/kg, $t = 3.12$, $p < 0.01$, post hoc comparison with *t*-test) persisted at the lowest dose level (0.05 mg/kg, $t = 2.68$, $p < 0.02$), but disappeared at higher doses (0.25 and 1.0 mg/kg). The suppression of grooming behavior by higher doses proved to be age-dependent and was present only in the young animals [significant effect of doses: $F(3,18) = 8.93$, $p < 0.01$, and age \times doses interaction: $F(3,36) = 3.69$, $p = 0.02$]. This experiment also served to select an optimal dose of 0.5 mg/kg AMPH for the cardiovascular and other behavioral studies. This dose was higher than the effective dose of 0.25 mg/kg but lower than the highest dose used (1.0 mg/kg), which evoked an exaggerated behavioral activation.

In a second behavioral experiment the age-dependency of AMPH effects on novelty-induced behavioral activity was studied in 5-, 21- and 33-month-old rats, representing young, aged and senescent ages (Table 1). A single dose of 0.5 mg/kg AMPH or saline was injected. The frequency of occurrence of exploratory movements, i.e., rearing, walking and head movements as well as that of grooming and immobility was statistically handled by two-factor ANOVAs comparing the two treatments and the three independent age groups, respectively. AMPH markedly influenced the expression of all behavioral items (effect of treatment, $p < 0.001$) except grooming which was only

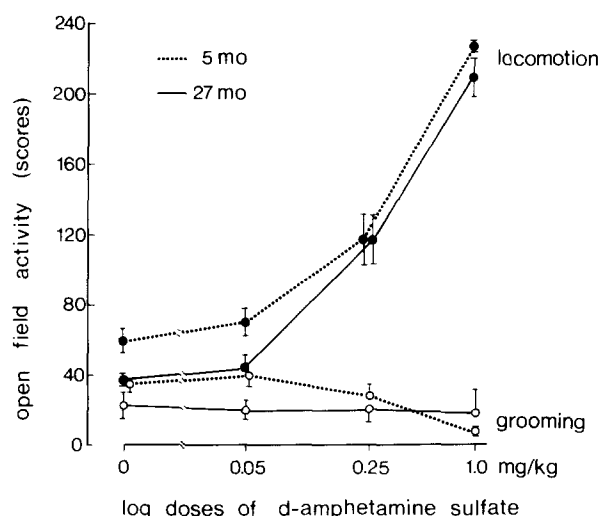


FIG. 2. Dose-dependent effects of d-amphetamine sulfate on locomotor and grooming activities of 5- and 27-month-old rats in the small open-field test. Means \pm SEMs are plotted from 7 animals per group. Locomotion scores are sums of rearing, walking, and head movement scores.

slightly changed ($p < 0.05$). With respect to rearing and head movements a significant age \times treatment interaction ($p < 0.001$) showed that young rats responded first of all with an increase in rearing activity, while senescent rats displayed more locomotor movements like head turnings and sniffing. Furthermore, AMPH treatment increased walking and decreased grooming without a significant age-dependency. Under drug-free conditions, the frequency of exploratory movement and grooming decreased, while immobility increased with age. Those behavioral parameters like walking and immobility, which were different in old (21 month) versus young animals (5 month), reached similar levels of appearance after AMPH. Immobility in senescent rats was greatly reduced by AMPH treatment but did not reach the same low levels as in adult rats.

Cardiac and Behavioral Effects of Amphetamine in Stress Versus Rest Conditions

The heart rate and behavioral data obtained in the two experimental conditions, emotional stress and rest, are shown in Fig. 3. A two-factor analysis of variance with repeated measures on one factor, sessions, was applied for statistical evaluation. The heart rate expressed as interbeat intervals was not significantly influenced by the age factor in the stress condition. In the home cage aged rats had a higher heart rate in the drug-free condition ($t = 2.27$, $p < 0.05$, post hoc *t*-test). Analysis of variance on pre- and postshock saline values revealed that only the 5-month-old animals responded to emotional stress with bradycardia [significant interaction between age and footshock, $F(1,12) = 18.9$, $p < 0.001$]. The heart rate change in aged rats was negligible. In contrast, both age groups displayed a comparable immobility in the emotional stress state indicating a learned behavioral response (61 and 64 percent significant decrease in activity of 5- and 27-month-old rats, respectively).

Treatment with 0.5 mg/kg AMPH induced a behavioral activation both in stress and in rest conditions. In the course of the postshock sessions a marked bradycardiac response appeared, $F(1,12) = 23.7$, $p < 0.001$, which was independent of age since no interaction between age and AMPH treatment was found.

TABLE 1

AGE-TYPICAL EXPRESSION OF AMPHETAMINE-INDUCED BEHAVIORAL ACTIVATION IN A SMALL OPEN-FIELD TEST

Behavior	Treatment	Age in Months		
		5	21	33
Rearing	AMPH	51.5 ± 7.8*¶	10.5 ± 3.0‡	5.6 ± 2.7‡
	Saline	26.1 ± 2.5	5.9 ± 1.7‡	1.6 ± 0.6‡
Walking	AMPH	58.5 ± 6.2¶	62.1 ± 6.6¶	42.4 ± 8.1*¶
	Saline	22.6 ± 2.9	11.3 ± 3.3†	6.8 ± 1.3†
Head turn	AMPH	82.1 ± 7.4¶	88.8 ± 10.3¶	114.9 ± 8.6‡¶
	Saline	47.5 ± 6.1	30.9 ± 4.5	15.6 ± 2.9‡
Grooming	AMPH	6.9 ± 1.7§	17.5 ± 7.1	7.9 ± 2.2
	Saline	21.0 ± 3.0	26.1 ± 7.5	11.6 ± 1.5†
Immobility	AMPH	40.3 ± 6.3¶	65.0 ± 14.5¶	70.4 ± 15.2*¶
	Saline	123.1 ± 8.8	164.6 ± 9.7‡	204.6 ± 6.8‡

*Mean ± SEM scores.

Each group contained 8 animals.

AMPH (0.5 mg/kg) was given 10 min prior to test.

† $p < 0.05$, ‡ $p < 0.01$ vs. 5-month-old rats (post hoc *t*-test).§ $p < 0.05$, ¶ $p < 0.01$ vs. age-matched saline control (post hoc *t*-test).

Young rats displayed an augmented bradycardia, while aged animals showed a clear bradycardiac response as compared to postshock saline control levels ($p < 0.01$, see Fig. 3). In the home cage, i.e., in the rest condition, although AMPH evoked behavioral activation it did not change heart rate values. The appearance of the bradycardiac response, therefore, was dependent on the experimental situation and only present in the stress condition.

Amphetamine and Systolic Blood Pressure in Stress and Rest Conditions

The effects of AMPH on SBP in stress and rest conditions are shown in Table 2. During stress there was no significant change in SBP across the postshock sessions in both age groups, although a slight SBP decrease after AMPH was observed. In rest conditions, however, there was an effect of AMPH, but only in aged rats. Two-factor ANOVA with repeated measures revealed a significant treatment effect in rest, $F(2,24) = 6.87$, $p < 0.005$, which was due to the hypotensive action of AMPH in the aged animals since a significant treatment × age interaction was also found, $F(2,24) = 3.87$, $p < 0.05$.

DISCUSSION

Bradycardia is a typical cardiac response in young adult rats to conditioned stress situations evoking behavioral immobility. This decelerated heart rate response does not occur during aging. The main finding of the present experiments is that in aged rats treatment with a low dose of AMPH restores the emotional stress-induced bradycardiac response, while the drug does not influence heart rate in rest conditions. This indicates that a state-dependent effect of AMPH can be attributed to an emotional stress factor and not to a generalized pharmacological action of AMPH. The lack of a bradycardiac response to emotional stress in aged rats confirms our earlier observations (27). In contrast to the heart rate response, aged rats showed the same behavioral immobility response in the conditioned avoidance situation as do young controls. Therefore, the lack of bradycardia after conditioned avoidance learning in aged rats is not due to a

TABLE 2

EFFECT OF AMPHETAMINE ON SYSTOLIC BLOOD PRESSURE (SBP) OF AGED AND YOUNG RATS IN STRESS AND REST CONDITIONS

	SBP (mmHg)			<i>p</i> -value
	Saline‡	AMPH†	Difference	
27 Month	139.4 ± 5.9*	132.4 ± 6.3	-7.0 ± 3.2	n.s.
Stress				
Rest	142.6 ± 7.1	127.9 ± 6.7	-14.7 ± 5.9	0.05
5 Month	148.8 ± 3.5	146.3 ± 4.9	-2.5 ± 5.6	n.s.
Stress				
Rest	142.8 ± 4.5	140.8 ± 5.0	-1.6 ± 2.1	n.s.

*Mean ± SEM.

†d-Amphetamine sulfate (0.5 mg/kg).

‡Mean of two saline sessions (7 and 10) preceding and following the drug session at day 8.

 $p < 0.05$ probability level (paired *t*-test).

memory deficit but to an autonomic dysregulation of heart frequency in response to emotional stress probably involving the vagus nerve (22,33). The baseline heart rate was higher in the aged rats suggesting a lower parasympathetic tone. The finding that the resting heart rate increases with age is consistent with some previous studies (22). Others, however, report no change (10) or a decreased heart rate in aged rats (6) indicating that this phenomenon may be strain dependent. In accordance with our current findings, studies in humans have also shown a reduced basal parasympathetic regulation of heart rhythmicity during senescence (29). In the presently used experimental design a relatively high heart rate could be observed in the dark-compartment of the avoidance setup, a situation in which both the aged and young nonstressed groups showed the same level of tachycardia. One may therefore conclude that the age-related suppression of parasympathetic cardiac response was not accompanied by an altered sympathetic unconditioned response in the aged rats.

The aged rats under drug-free conditions did not react to emotional stress with bradycardia, but performed the bradycardiac response at similar levels as young animals under the influence of AMPH. The AMPH treatment apparently reinstated the stress-induced vagal activation in aged rats and increased the amplitude of the response in young rats. Measuring locomotor activity during ECG recording in the stress situation after AMPH treatment clearly showed that both aged and young rats increased their activity to a comparable level. From a physiological viewpoint one would expect an increased heart rate of drug-treated rats as a result activation by somatic coupling (28). The present findings, however, indicate that cardiac rhythmicity is not automatically adjusted to somatic activity, but is apparently dominated by psychosomatic regulation processes in emotional stress conditions (8,27).

To obtain a more detailed picture of the autonomic response to AMPH in aged rats, the systolic blood pressure was also measured. The SBP was determined in relation to the heart rate values and measured immediately after the ECG sampling, i.e., approximately 25 min after the drug/saline injections. Amphetamine had no significant impact on SBP levels measured in stress conditions in either age groups. In the rest condition the 27-month-old rats showed a slightly lower SBP level when treated with AMPH. It is therefore unlikely that facilitation of the bradycardiac response of the AMPH-treated rats did result from a simple baroreceptor reflex activation.

The behavioral immobility response in the dark-compartment

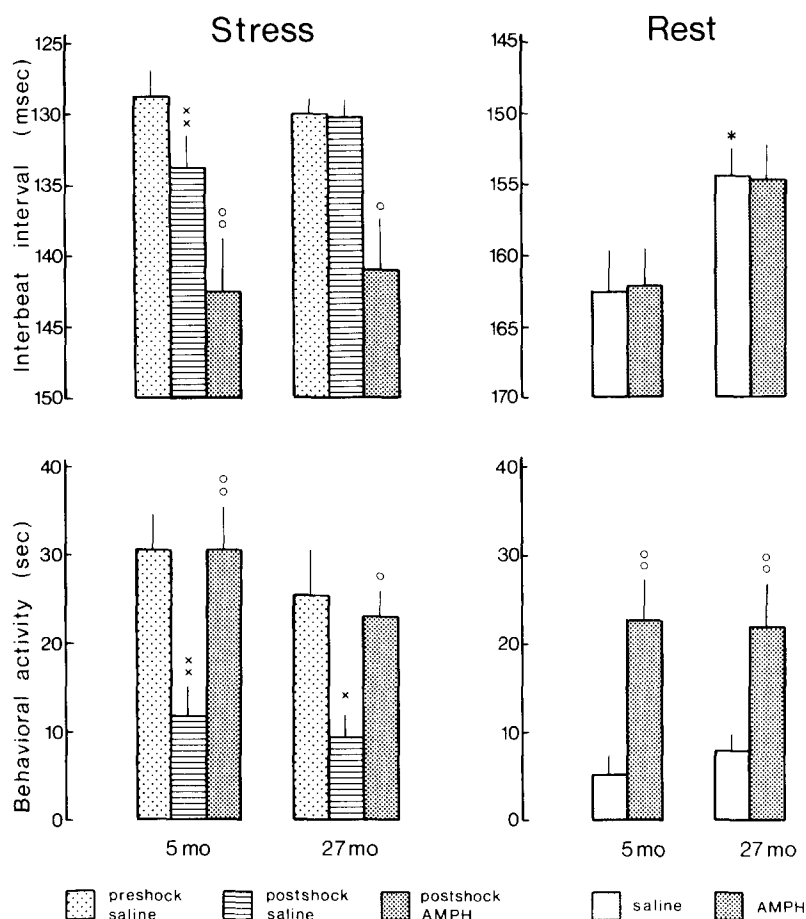


FIG. 3. Cardiac and behavioral effects of low dose AMPH (0.5 mg/kg d-amphetamine sulfate) in young and aged rats. Heart rate expressed as IBI and behavioral activity are shown in stress and rest (home cage) conditions. Data are means \pm SEMs from 7 animals per group. Columns represent the following sessions: under the heading "stress": preshock saline—day 5, postshock saline—averaged values from days 7 and 10, postshock AMPH—day 8; under the heading "rest": saline—averaged values from sessions 3 and 6, AMPH—session 4 (see also Fig. 1). Paired *t*-test was used to compare data sets of adjacent columns after completion of two-factor ANOVAs with repeated measures on sessions: ***p* < 0.01 vs. preshock saline control, °*p* < 0.05 and °°*p* < 0.01 vs. postshock saline control, **p* < 0.05 vs. saline-treated young rats in the home cage.

the day after the footshock, was considered as a sign of successful learning and memory processes. In this respect the 27-month-old rats performed similar as the younger counterparts. In our previous study (27) a deficit in passive avoidance learning could be observed only in senescent rats above the age of 30 months. Depending on the complexity of the task, the behavioral paradigm used, the experimental circumstances, but also on the exact age of experimental animals, aging rats may show deficits in their capacity for learning and memory (14, 17, 31, 38). Both the presence and lack of cognitive deficits in aging animals should be viewed with appropriate criticism since motor or sensory dysfunctions might also be present and influence cognitive performance (14,31). The psychostimulant AMPH has been reported to facilitate learned behavioral responses not only in young but also in aged rats (11). Moreover, deficient motor coordination, which may hamper learned responses, could be antagonized with central dopamine receptor stimulation in aged rats (24). These latter studies and our present results with AMPH indicate that age-related decline in performance may for a consid-

erable part be attributed to a deterioration in the central control mechanisms underlying cognitive and motor functions.

In general, the behavioral activation in response to novelty decreases with age (5, 14, 16, 34), suggesting a deficient behavioral arousal. Some authors (5) observed a delay in behavioral arousal, while others described an age-related shift in the type of behavioral response to novelty (34). This is also apparent from age-related differences in the composition of movement patterns in response to novelty in the present study. A reduced behavioral arousal in aged rats is indicated by the observations on the 21-, or 27-month-old animals showing a series of behavioral signs of reduced novelty-induced small open-field (SOF) activity. This behavioral suppression was even more pronounced in the senescent 33-month-old rats.

The behavioral activation due to AMPH treatment showed an age-typical appearance. Induction of rearing responses decreased with age, while aged rats performed more hypokinetic types of motor movements like head turning and sniffing. Amphetamine abolished the higher incidence of immobility of 21-month-aged

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